Anticancer drugs Part 2

Pharmacology 3

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Anticancer Drugs

1. **Cytotoxic agents**

- بسم الله نبدأ..

Cytotoxic agents is the highly agent that causing toxicity beacause it NOT بعتبر الـ distingueshed between cancer cell and Normal rapidlly proliferation cell.

2-Targeted therapy

- تعتبر highly effective، وتُعتبر أهون من الـ Cytotoxic agents (يعني هي low incidance compare with cytotoxic agents)

.3Hormones and related compounds

Cytotoxic agents

- وعندي من هاي العائلة أدوية سواء كانت specefic action Or Non specefic action.

1) Alkylating agents and related compounds بعتبرها Non specefic action
2) Antimetabolites تستهدف الـ S phase
3) Cytotoxic antibiotics بحكيها Antibiotic عشان الـ source تبعها جاي من Plant.
4) Plant derivatives: vinca alkaloids, taxanes.

Alkylating agents

بالميديسنال صغاري رح تنهروا عنهم هدول، بس عشان امتحان الفارما قبل الميديسنال رح أوضّح أكثر..

سميتها Alkylating agents عشان الـ Alkyl group بتربُط مع الـ DNA of cancer cell ✓

1) Nitrogen mustards: chlorambucil, cyclophosphamide, mechlorethamine كانت تُستخدَم كأسلحة غازية في الحرب العالمية الأُولى
2) Nitrosureas: carmistine, lomustine
3) Alkylsulfonates: busulfan
4) Platinum analogs: cisplatin, carboplatin, and oxaliplatin
5) Other Alkylating Agents: dacarbazine, procarbazine, & bendamustine

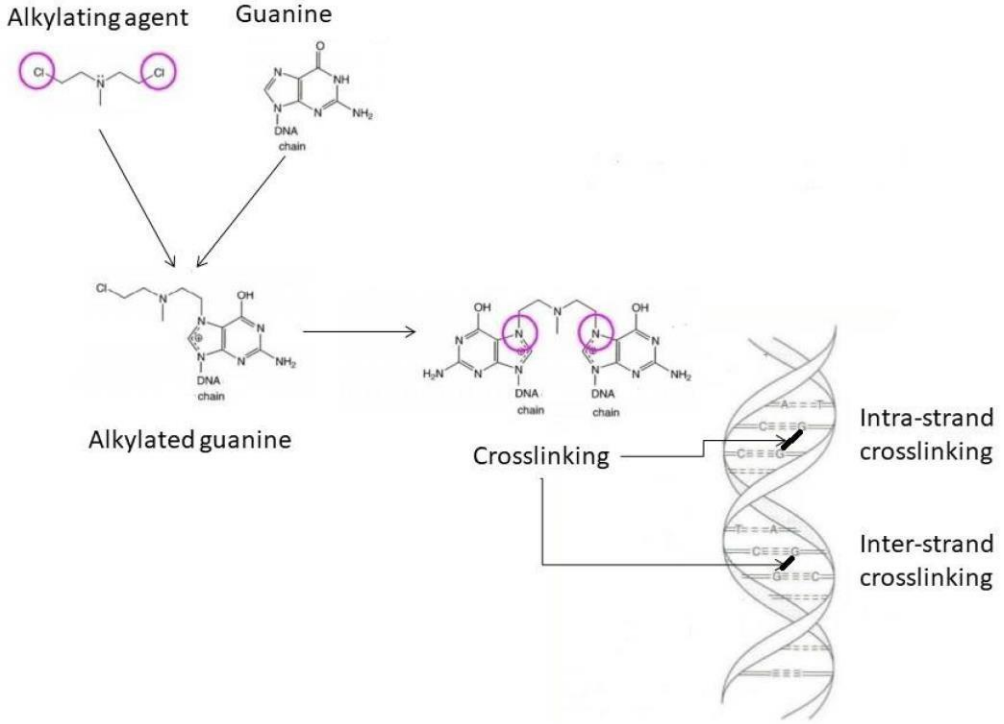
- والدكتورة حكت بس رح تشرح عن مجموعتين (الباقي ما بدها تفاصيله، يعني محذوف كتشير أوي يا كتاكيتي 😂♡)

Mechanism of actions

- Form reactive molecular species that transfer of their alkyl groups to various cellular constituents
- The macromolecular sites of DNA, includedamagealkylation

  RNA, proteins, and various enzymes
- Alkylations of DNA within the nucleus represent the major

  interactionsthat lead to cell death



بشكل عام صغاري :
الـ Mechanism of action تستهدف الـ guanine in DNA of cancer cell .
وتعمل Cross linking يا إمّا intrastrand (على نفس الـ strand)، أو interstrand (بين سلسلتين).
وهاد الارتباط بعمل عندي dysfunction of cell cancer
وبالتالي بحفِّز عندي موت الخلية السرطانية.

ومُمكن هاد الـ Cross linking يصير in any stage of cell cycle ✓.

Alkylating agents

- Are cell cycle-nonspecific

- وعشان هيك بحكيلها Non specefic action.

- Primarily effective against rapidly proliferating cells.

- المُشكلة هون إنّه عندي Normal rapidly cell proliferation بتتأثَّر بهاي الأدوية in s phase (فبشكل رئيسي صغاري هاي الأدوية بتعمل DNA damage). phase1 and G

- Used in combination with other agents to treat a wide variety of lymphatic and solid cancer.

- أصلاً وإجمالاً يعني أدوية السرطان ما بتتاخذ بشكل فردي، يعني هي بالغالب in combination.

- Are mutagenic and carcinogenic and can lead to secondary malignancies

- هاي الـ adverse side effects مُشتركة بين كُل أدوية الكانسر، وخاصّةً الـ Cytotoxic agents، عشان هيك ممنوعين للمرأة الحامل ؛ لأنها بتعمل تشوُّهات جنينة.

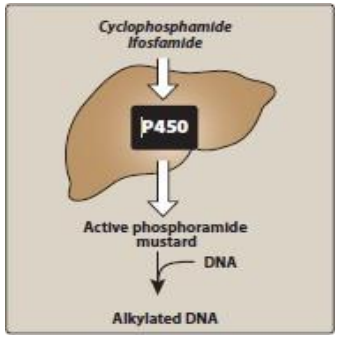
Cyclophosphamide

- Activated hepatically 4-hydroxy cyclophosphamide.

- بحاجة لـ activation by liver ✓

- The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein.

Phosphoramide (active cytotoxic) Acrolein (haemorrhagic cystitis)



- مُشكلتي مع هاد الدوا هي بالـ cytotoxic metabolites اللي بنتج عن الـ metabolism تبعته

- Haemorrhagic cystitis is minimized by:
  - high fluid intake & Irrigation of the bladder with:

- بعمل عندي inflammation in bladder، وبحل هاي المشكلة يا بالـ MESNA يا بالـ Alkaline of urine.

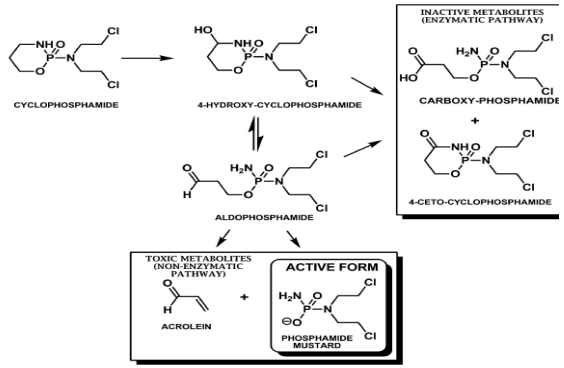


FIGURE 13 - Diagram of cyclophosphamide bioactivation.

N-acetyl cysteine or N_2 mercaptoethane sulfonate (MESNA) → non toxic complex with acrolein.

- شايفين صغاري الجُملة اللي بالأخضر فوق بدهاش إياها الدكتورة، حكت احفظوا بس إنّه MESNA (قال يعني لو ما حذفته كان حفظناه 😂💔) هاد الـ MESNA بعمل complex with acrolein، وبمنع الـ adverse Effects اللي بعمله الـ acrolein وبنعطى IV.

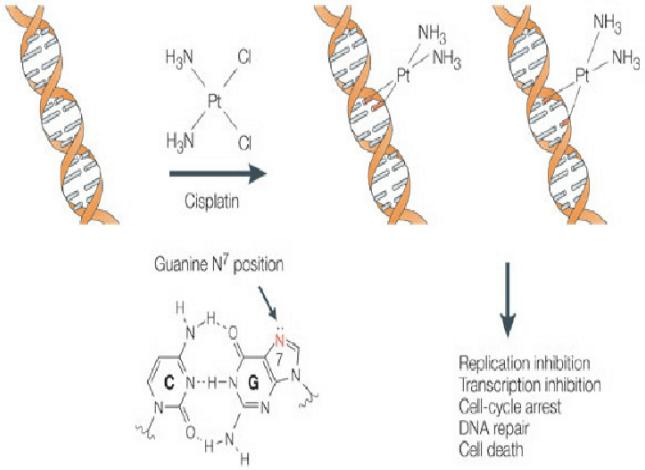
- Other ADRs: Alopecia, NVD, Bone marrow suppression

Platinum analogs (cisplatin, carboplatin, & oxaliplatin)

- مُمكن أعتبر الـ Nephrotoxicity with cisplatin is reversibly

1) First generation: Cisplatin ✓ complex with guanine in DNA of cancer cell - برضو يا كتاكيتي هاد بعمل

- ويعتبر الـ cisplatin is the highly combination with Nephrotoxicity-



- because of its severe toxicity, *carboplatin* was developed.
- ADEs:
- Renal toxicity (major) and can be prevented by aggressive hydration

- الفكرة هون إنّه عشان نحمي شوي الكلى من وحشية الـ cisplatin بحكي للمريض يهتم بالـ hydration شوي، لكن لو المريض معه ضغط أو congestive heart ساعتها بعمل fauiler switch from cisplatin to Other Anti cancer.

ونفس اللي قبله يا intrastrand OR interstrand، وبالأخير بعمل DNA damage.

- N and V - أسوأ دوا بعمل N and V is cisplatin.
- Hearing loss (10 to 30% of patients)

-وشيء كثير مُهم : بالمنطق صغاري ما بنفع أبداً تروح تعمل combination between cyclophosphamide and cisplatin، والسبب إنّه الدوايين هدول بحاجة hydration، فأكيد مش رح احكي للمريض اشرب قارورة مي باليوم هيبقى منظرنا وحش كصيادلة والله ☺

Platinum analogs (carboplatin, & oxaliplatin)

2) Second generation: Carboplatin

- نفس الـ MOA of cisplatin، لكن يعتبر الأفضل من حيث أقل side effects, especially in Nephrotoxicity and ototoxocity.

- MOA, mechanisms of resistance, and clinical uses are identical to cisplatin.
- Carboplatin is used when patients cannot be vigorously hydrated, as is required for cisplatin treatment or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity.

- لو المريض وضعه سيء بقصة أخذ الـ Hydration، مُمكن أعمل ☑ switch from cisplatin to carboplatin

- it exhibits significantly less renal toxicity and gastrointestinal toxicity, peripheral nerves, and hearing loss.
- It is more myelosuppressive than cisplatin.

3) Third generation: oxaliplatin

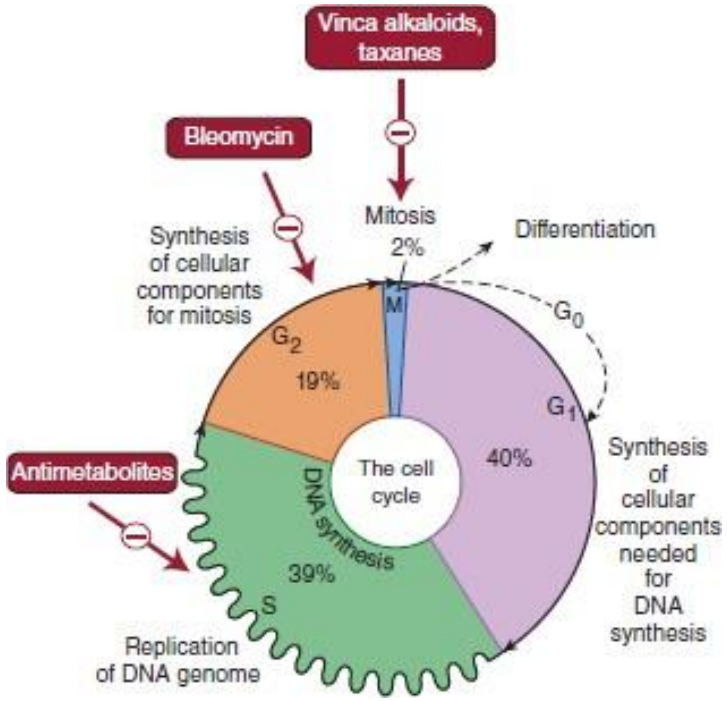
- Similar to cisplatin and carboplatin.
- ADEs: Neurotoxicity manifested by a peripheral sensory neuropathy

- لأ هاد مشكلته بالـ Neurotoxicity (أنتو وين ما تشوفو كلمة toxicity اختاروها بالامتحان ☺)

Antimetabolites

.The fisrtt cell cycle specefic action

- They act primarily in S phase
- Are structurally similar to endogenous compounds
- These drugs can compete for binding sites on enzymes or can themselves become incorporated into DNA or RNA and thus interfere with cell growth and proliferation.



شغّالين على الـ purine and pyrmidine analogs.

Antimetabolites

Folate antagonist:	Methotrexate (Mtx).
Purine antagonist: .Purine = Adanine and guanine	6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine, Fludarabine.
Pyrimidine antagonist: **Pyrmidine =Uracil**	5-Fluorouracil (5-FU), Capecitabine Cytarabine (cytosine arabinoside).

Folate antagonist-Methotrexate (MTX)

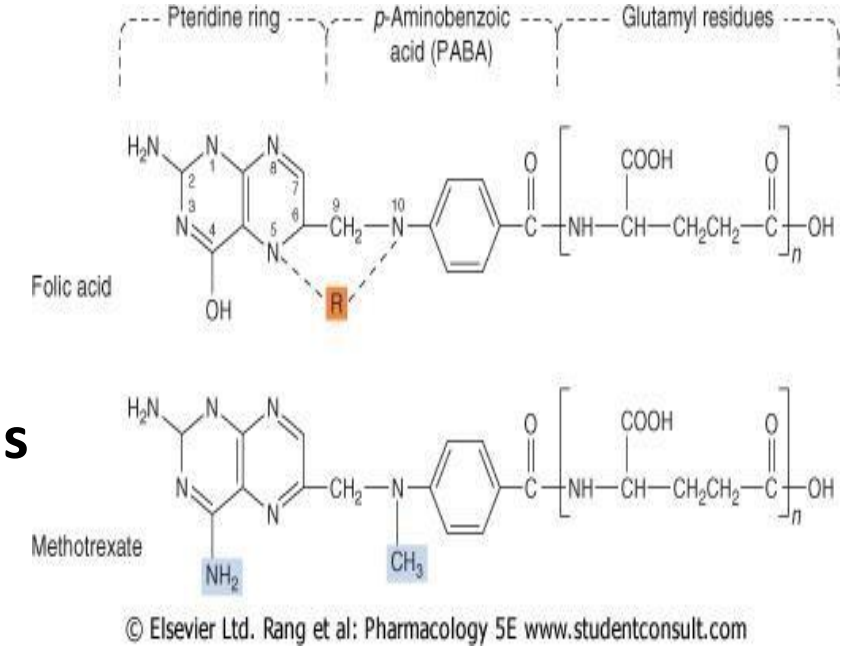
- الستركشر تبعه similar to folic acid.

- MXT competitively inhibits the binding of folic acid to the enzyme dihydrofolate reductase (DHFR)
- It interferes with the synthesis of tetrahydrofolate (FH_4), This action leads to a decrease in the synthesis of

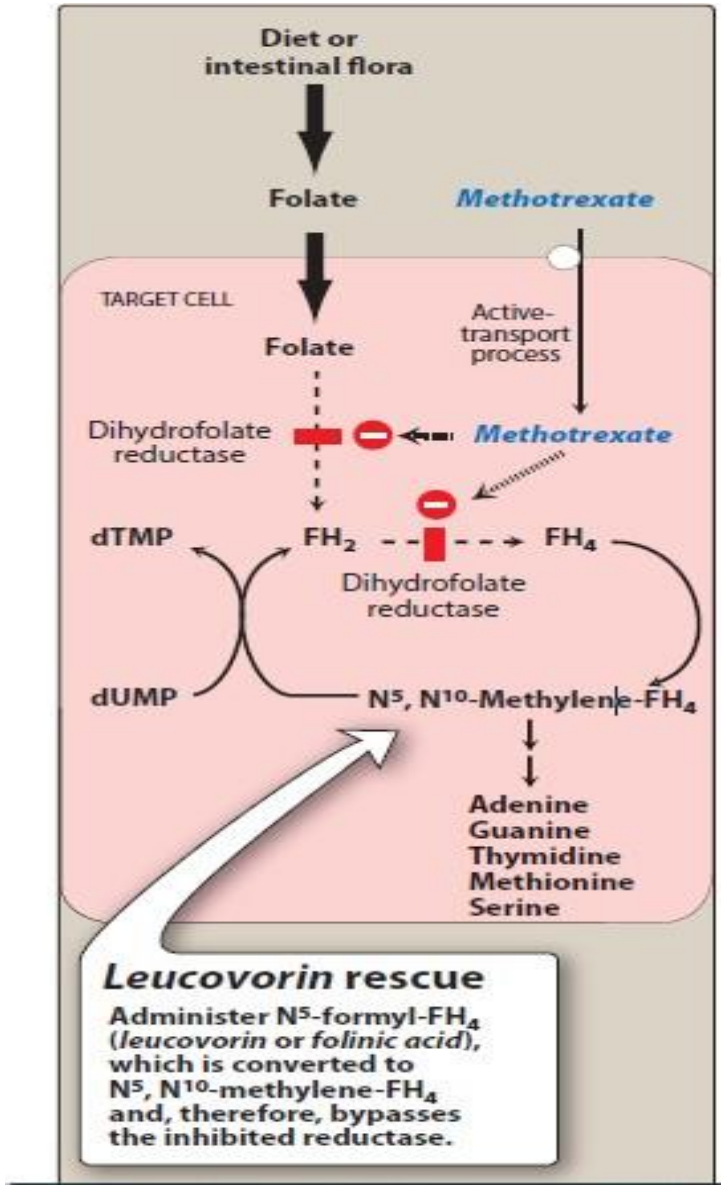
thymidylate, purine nucleotides, and amino acids and

thus interferes with nucleic acid and protein

metabolism



-طبعاً صغاري مُتنا وإحنا بنحكي إنّه الـ folinlic acid اللي هو نفسه الـ THFA، كثير مُهم لبناء الـ DNA.



The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH2), or by administration of *leucovorin,* which bypasses the blocked enzyme and replenishes the folate pool.

- وسُبحان الله كتاكيتي الـ leucovorin بصرله امتصاص من النورمال سيل أكثر من الكانسر سيل.

مُشكلتي أنا مع هاد الدوا إنّه decrease level of folinlic acid in cancer cell and Normal cell، وبحل هاي المشكلة بإني آخُد folinlic acid ✓.

Folate antagonist-Methotrexate (MTX)

- Therapeutic uses usually in combination with other drugs as anticancer.
- low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis.

- Pharmcokinetics: is administered by the intravenous, intrathecal, or oral route. However, oral bioavailability is saturable and erratic at doses greater than 25 mg/m2.
- Renal excretion is the main route of elimination. aspirin, nonsteroidal anti-inflammatory agents, penicillin, and cephalosporins, as these agents inhibit the renal excretion of MTX

Folate antagonist Methotrexate (MTX)

-is classefied as category X in pregnancy

1. **GIT: NVD, ulcerative mucositis, stomatitis**
2. **bone marrow suppression**
3. **Alopecia**

.4 Dermatitis. metabolism by liver بصرله وبالتالي بروح على الجلد وخُدلك التهابات عفق.

Can be prevented or reveresed by administration of folinic acid (leucovorin) “leucovorin rescue”

Folate antagonist-Methotrexate (MTX)

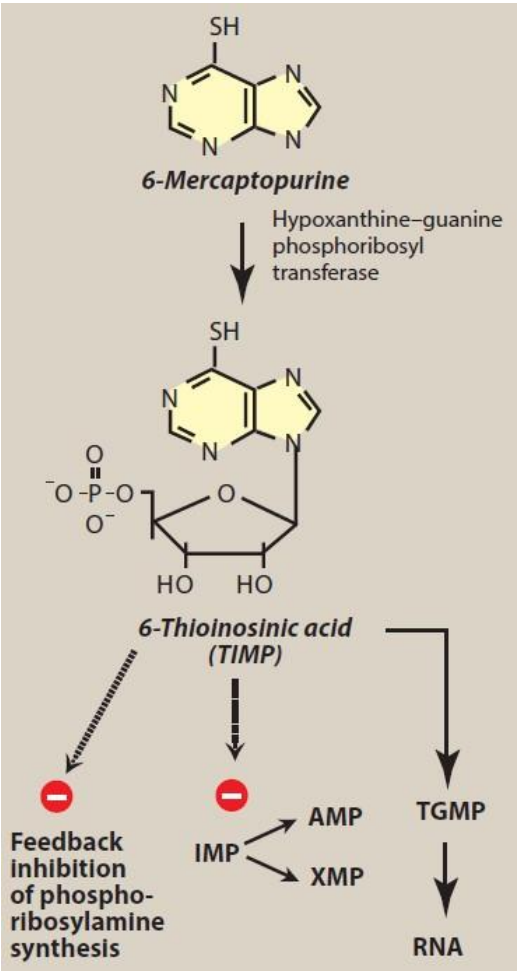
5. ***Renal damage:*** **Alkalinization of the urine and adequate hydration can help**
6. ***Hepatotoxicity:*** **cirrhosis (long-term use)**

7. ***Pulmonary toxicity:*** **infiltrates and fibrosis.**

Purine antagonists

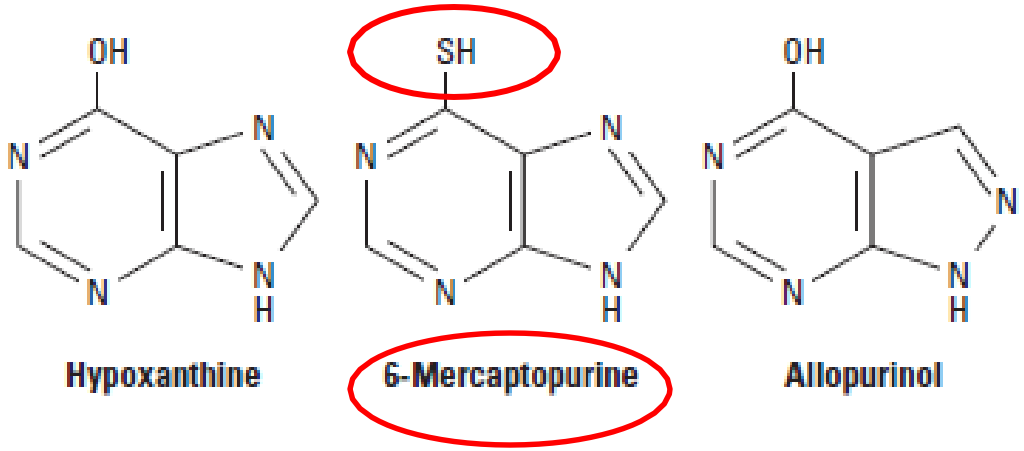
- Purine analogues: 6- Mercaptopurine (6-MP) & 6-thioguanine (6-TG)
- Both are activated intracellularly by hypoxanthine-guanine phosphoribosyl transferases (HGPRT) to the ribonucleotides 6-thioguanosine-5′-monophosphate (6-thioGMP) & 6-thioinosine-5′-monophosphate (TIMP)
- Nucleotides formed from 6-MP and 6-TG and synthesispurinenovodeinhibit also become incorporated into nucleic acids

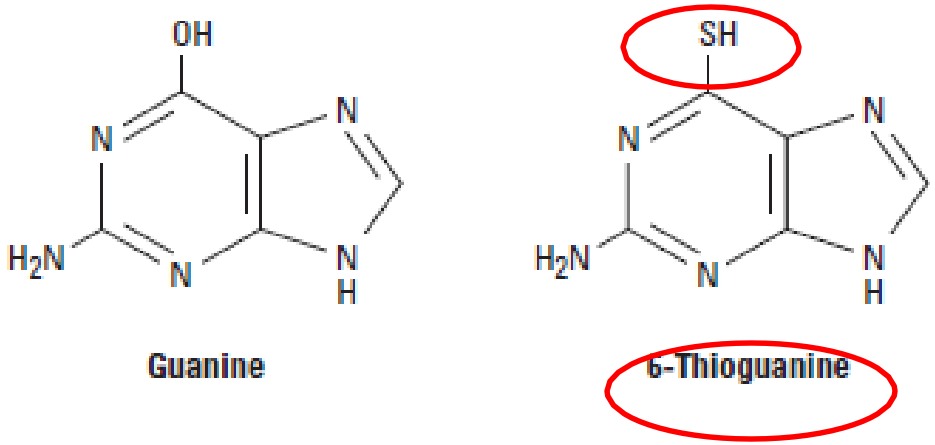
بتعمل Active metabolites of purine antagonist بس اعرفوا إنّه الـ -
De novo of the DNA and RNA in nucleic acids in the cells



Actions of 6-mercaptopurine. GMP = guanosine monophosphate; AMP =adenosine monophosphate; XMP = xanthosine monophosphate.

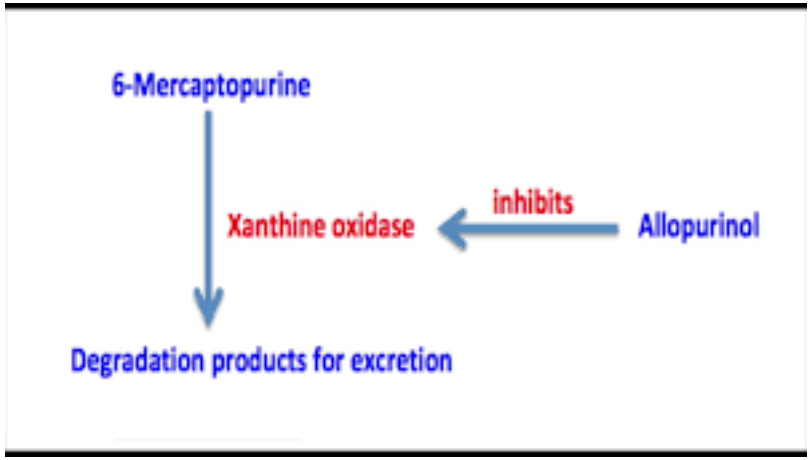
Purine antagonists





Purine antagonists

- **Pharmacokinetics:**
- **Absorption by the oral route is erratic and incomplete.**
- **The bioavailability of 6-MP can be reduced by the first-pass metabolism in the liver**
- **6-MP is converted to an inactive metabolite (6- thiouric acid) by an oxidation reaction catalyzed by xanthine oxidase.**



- هاي الأدوية بصرلها convert from active to inactive by xanthine oxidase which can be inhibeted by allopurinol..
- وبعطي الـ allopurinol لمرضى الكانسر عشان تكسير الخلايا عندهم كبير
- لو عملت combination between 6-mercaptopurine and allopurinol بكون عملت زيادة بالـ half life of Methotrexate وبنفس الوقت منعت ارتفاع اليوريك أسيد.

Purine analogues

- Potential D-D interaction with xanthine oxidase inhibitor (allopurinol): the dose of 6-MP must be reduced by 50–75%

  6-TG dose not interact with allopurinol

  - ADEs: bone marrow suppression toxicity & hepatic dysfunction
  - Bone marrow suppression is less common with 6-TG